OC-0399

Dose to heart substructures is associated with non-cancer death after SBRT in stage I NSCLC patients

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Purpose or Objective: For NSCLC patients treated with SBRT, we investigated if dose to the heart and its substructures is associated with non-cancer death.

Material and Methods: From 2006-2013 801 patients with early stage NSCLC were treated with CBCT guided SBRT (median 54 Gy in 3 fractions) in 5 institutes for whom treatment plans were available. 565 patients were analyzed after exclusion of synchronous or metachronous tumors (n=80), follow-up<1y (n=63), or death from cancer (93).An average anatomy was constructed based on 109 patients of the 5 institutes using deformable image registration. Subsequently, all patients were registered to this average anatomy and the corresponding dose distribution was deformed accordingly [1]. The heart and substructures right atrium, left atrium, right ventricle, left ventricle, superior vena cava, descending aorta and left pulmonary artery were contoured on the average anatomy. For each (sub)structure dosimetric parameters DV (V: 0 cc-max), VD (D: 0 Gy-max), EUDn (n: 0.1-10) were obtained.Associations of these dosimetric parameters with death were evaluated using univariate Cox regression. Per (sub)structure the parameter with the lowest Akaike information criterion was selected and used in subsequent analyses. Correlations between all (sub)structures were assessed prior to inclusion in a multivariate Cox regression. Finally, the (sub)structure(s) that remained significant in the first multivariate analysis were included in a second multivariate analysis, also including; performance status, age, gender, biological dose, distance to bronchus, comorbidity index, lung-function, tumor diameter, T-stage, institute and pack years smoking.

Results: With a median follow-up of 28 months, 58% of patients were alive. 3% had a central tumor. Univariate analysis showed significant associations between the (sub)structures and death. The most predictive parameters per (sub)structure are shown in table 1. Correlations between the heart and it's substructures was strong (average 0.7). As dose to the heart was also represented by dose to the heart substructures, heart_D0 was not included in the multivariate analysis. Maximum dose to the left atrium and dose to 2 cc of the superior vena cava were significant in the multivariate analysis (p=0.033, HR=1.012 and p=0.034, HR=1.022 respectively). Association between survival and these parameters is shown in figure 1.In the second multivariate analysis these parameters remained significantly associated with death, as well as age (p<0.001, HR=1.034), performance status(p=0.004, HR=1.138), comorbidity index (p=0.032, HR=1.125), lung-function (p<0.001, HR=0.984) and pack years smoking (p=0.004, HR=1.011).

Structure	p-value	Akaike Information Criterion
Heart_D0	0.007	2707.626
Left atrium_D0	0.003	2706.557
Left ventricle_V0.5	0.049	2710.475
Right atrium_D0	0.008	2708.078
Right ventricle_D5	0.008	2708.555
Superior vena cava_D2	0.003	2706.694
Left pulmonary artery_D10	0.014	2708.812
Descending aorta_D10	0.023	2709.512

Table 1. Most predictive (sub)structures and corresponding p-values and Akaike Information Criterion

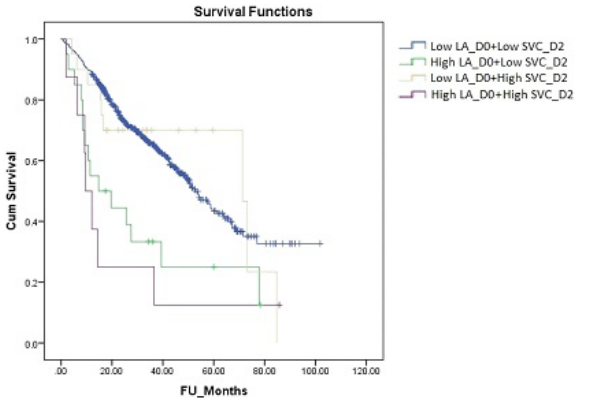

Figure 1. Survival associated with maximum dose to the left atrium (LA_D0) and dose to 2cc of the superior vena cava (SVC_D2). Both parameters split at 95th percentile.

Conclusion: For these NSCLC patients treated with SBRT we found significant associations between non-cancer death and the maximum dose on the left atrium, and to the D2cc of the superior vena cava. Consequently, heart sparing potentially improves outcome.

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OC-0400

Risk estimation of cardiac toxicity following craniospinal irradiation of pediatric patients.

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Purpose or Objective: Craniospinal irradiation (CSI) plays an important role in the treatment of medulloblastoma and improvement in treatment during the last decades has resulted in good prognosis. CSI is most commonly delivered with photons or a combination of photon/electrons. However, proton therapy is generally indicated as it lowers the dose to normal tissues and potentially reduces the risk of late effect. The aim of this study was therefore to compare the estimated risk of cardiac toxicity following CSI using photons, electrons and protons.

Material and Methods: CSI treatment plans including conformal photons, electrons/photons combined, double scattering protons (DS) and intensity modulated proton therapy (IMPT) were created in the Eclipse treatment planning system [Varian Medical Systems, Palo Alto, CA, USA] for six pediatric patients. The CTV included the brain and the spinal canal, for the protons the CTV was expanded to also include the entire vertebral body to prevent asymmetric growth of the skeleton. During treatment planning a setup uncertainty of 5 mm was taken into account, as well as an uncertainty in the proton range of 3.5 %. The prescribed dose for all techniques was 23.4 Gy(RBE). Dose-risk models derived from two independent pediatric patient cohorts were used to estimate the risk of cardiac toxicity. The excess Relative Risk (ERR – relative to general population) for cardiac mortality was estimated using a linear model [1], while ERR for cardiac failure and disorder were estimated using both a linear and a linear-quadratic [2] (LQ) model. Input parameters were the mean heart dose, and the parameters (with 95 % Confidence Interval (CI)) displayed in Table I. The Relative Risk (RR) was

defined as the ratio between ERR for photon /electron, photon/DS and photon/IMPT.

Table I: Dose-response models, parameters and 95 % CI

	Model	Parameter	95 % CI
Mortality	Linear[1]	α: 0.6	0.2; 2.5
Disorder	Linear[2]	α: 0.35	-0.005; 1.2
	LQ	α_1: 0.4	0.002; 1.4
		α_2:-0.00013	-0.01 ;0.1
Failure	Linear[2]	α: 0.09	-0.02; 0.3
	LQ	α_1: 0.19	-0.02; 0.5
		α_2: -0.002	-0.004; 0

Results: Regardless of dose-risk model applied, the conformal photons were ranked with the highest ERR for all cardiac toxicities, whereas IMPT was ranked with the lowest (Figure 1a). For cardiac mortality the ERR for photon was 8.1 (95 % CI: 3.4 to 30.5), while ERR for IMPT were 1.3 (95 % CI: 1.1 to 2.4). For cardiac disorder and cardiac failure the ERR for photon was 5.1 (95 % CI: 0.9 to 15.2) and 2.1 (95 % CI: 0.8 to 4.6), respectively (Linear model). The corresponding results for IMPT were 1.2 (95% CI: 1.0 to 1.7) and 1.1 (95 % CI: 1.0 to 1.2). Similar trends were found using the LQ model. Relative to IMPT, photons lead to a risk of cardiac mortality that was a factor of 6.1 higher (range 5.7 to 7.0), cardiac disorder a factor of 4.3 higher (range 4.1 to 4.9) and cardiac failure a factor of 2.0 higher (range 1.9 to 2.1) (Figure 1b).

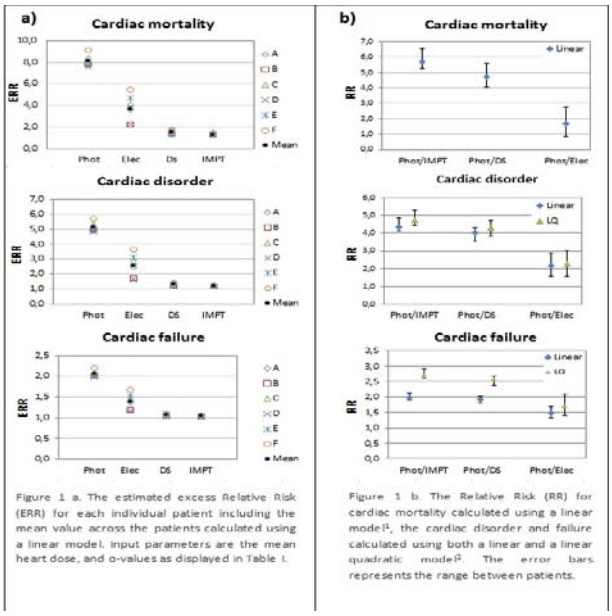

Figure 1 a. The estimated excess Relative Risk (ERR) for each individual patient including the mean value across the patients calculated using a linear model. Input parameters are the mean heart dose, and α-values as displayed in Table I.

Figure 1 b. The Relative Risk (RR) for cardiac mortality calculated using a linear model[1], the cardiac disorder and failure calculated using both a linear and a linear quadratic model[2]. The error bars represents the range between patients.

Conclusion: Across different cardiac morbidity endpoints, and despite different dose-risk models used, the results of our modelling study were consistently in favour of protons.

References:
1. Clin Oncol, 2010: 28 (8): 1308-1315
2. Radiother and Oncol: 2006 (81): 47-56

Symposium: Emerging biomarkers

SP-0401

Circulating tumour cells as biomarkers in lung radiotherapy

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It has long been hypothesized that the propagation of circulating tumour cells (CTCs) is a pre-requisite for the development of metastases. However, robust technology to reliably isolate CTCs and characterise them at the molecular level has only become available in recent years. Thus repeated blood sampling for CTCs could provide a non-invasive method of serially reassessing tumour status and evolving tumour biology.

Patients with stage I-III NSCLC are at high risk of developing distant metastases after radiotherapy (RT) or chemo-radiotherapy treatment. With the advent of new technologies to enumerate CTCs, the clinical significance of CTCs before, during and after RT has become of great interest. In the current era of targeted therapy and the development of personalised medicine the question still remains as to whether CTCs could be used to identify patients most likely to benefit from radical RT and prevent the delivery of futile cancer treatments and their associated toxicity. Prospective clinical trials have shown the prognostic value of CTC enumeration in patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (1, 2). Although CTCs have been used as a surrogate biomarker in hundreds of clinical trials, as yet none have been incorporated into standard clinical practice. To date there are few published studies evaluating CTC's in patients undergoing radical thoracic RT.

In my talk I will discuss the following:

•novel platforms available for isolation of CTCs

•current data on the evaluation of CTCs as a biomarker in NSCLC and SCLC patients treated with RT

•advantages and limitations of CTCs as a biomarker •future directions and the prospect of using CTCs to stratify patients in clinical trials

References

ADDIN EN.REFLIST 1. Krebs MG, Sloane R, PriestL, Lancashire L, Hou JM, Greystoke A, et al. Evaluation and prognosticsignificance of circulating tumor cells in patients with non-small-cell lungcancer. Journal of clinical oncology : official journal of the American Societyof Clinical Oncology. 2011 Apr 20;29(12):1556-63. PubMed PMID: 21422424.

2. HouJ, Krebs M, Lancashire L, Sloane R, Backen A, Swain R, et al. ClinicalSignificance and Molecular Characteristics of Circulating Tumor Cells andCirculating Tumor Microemboli in Patients With Small-Cell Lung Cancer. Journalof Clinical Oncology. 2012 FEB 10 2012;30(5):525-32. PubMed PMID:WOS:000302622900018. English.

SP-0402

The fall and raise of predictive radiotherapy biomarkers

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Radiotherapy is a mainstay of cancer treatment. Due to it high efficacy to inactivate cancer stem cells in the primary tumor and regional metastases as well as its increasing ability to spare normal tissues, it has a proven curative potential in